REMARKS

Claims 58-93 are currently pending in this application. All of the pending claims have been rejected. By the present amendment, claims 60-62, 72-73, 75-76, 80-81, 83-84 and 88-89 have been amended. Support for the amendment can be found throughout the entire specification. No new matter has been added, and the amendment is made without prejudice or disclaimer of any cancelled subject matter.

Each of the rejections raised by the Examiner in the Office Action dated August 28, 2002, are discussed below.

Double-patenting Rejection

Claims 60-92 have been rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1-25 of US Patent No. 6,251,590, in view of Chee et al. If the pending claims are found to be otherwise allowable except for this ground of rejection, Applicants will submit an appropriate terminal disclaimer. In this event, Applicants request that the Examiner telephone the undersigned who will then provide the terminal disclaimer.

Claim rejection under 35 U.S.C. § 112, first paragraph

Claims 60-63 and 72-93 have been rejected under 35 U.S.C. § 112, first paragraph, for lack of an adequate written description. In rendering the rejection, the Examiner admits that the specification teaches methods of obtaining nucleic acids that correspond to spliced regions, but contends that it does not provide sufficient support for product claims. The Examiner indicates that "*there is no description of all the possible varying spliced exons, introns and junctions. The general knowledge in the art concerning spliced variants does not provide any indication of how the structure of one spliced variant within a single gene would be representative across all genes in all organisms. The nature of spliced genes is that they are variant structures and the present state of the art the structure of one does not provide guidance to the structure of others.*" Applicants respectfully traverse the rejection.

a) Introns share common attributes

It has been reported in the art that splicings occur through particular mechanisms which involve *cis* and *trans* elements. Cis elements are carried by the RNA itself, such as splice acceptor (SA) sites and splice donor (SD) sites. In this regard, it is known that introns are flanked by conserved consensus sequences. More specifically, introns start with a GU pair (5'-end) and end-up with a GA pair (3'-end). Introns also contain sequences for binding of *trans* elements, which are typically composed of an Adenine and a stretch of Pyrimidines. These sequences and motifs characterize introns, which thus share common attributes.

b) The specification teaches spliced regions and broad methods of obtaining such nucleic acids

The specification teaches the identification of various splicing events. In particular, Example 1.4. illustrates the identification of 34 clones comprising spliced regions specific for apoptotic cells and of 13 clones comprising spliced regions specific for growing cells (see page 49, lines 1-3). A specific example of such clones is ΔSHC, whose sequence is provided in the sequence listing. Example 2 shows the identification of Grb33. Example 4.5 shows the identification of sequences "specifically expressed during potent p53 induction which leads to cell death (Figure 16)." As indicated, these clones derive from exon or intron sequences (see page 57, lines 1-4). Example 5 further illustrates the identification of particular spliced nucleic acid sequences (see in particular page 60, lines 20-30 and Figure 19). Accordingly, the application is not limited to a working example Gbr2 spliced forms, as mentioned by the Examiner, but illustrates the identification and cloning of various nucleic acids corresponding to spliced domains.

Furthermore, the application discloses in great details methods of obtaining such nucleic acids. These include cross hybridisation reactions, as claimed in allowed parent case U.S. Patent No. 6,251,590 as well as oligonucleotide design approaches, as disclosed for instance page 23 of the application:

"These oligonucleotides may for example be generated according to the following strategy :

(a) identifying a protein or a splicing event characteristic of an apoptotic condition and the sequence of the spliced domain. This identification procedure can be based upon published data or a compilation of available sequences in databases;

(b) synthesizing artificially one or more oligonucleotides corresponding to one or more regions of this domain, which therefore allow the identification of the unspliced form in the RNAs of a test sample through hybridization ;

(c) synthesizing artificially one or more oligonucleotides corresponding to the junction region between two domains separated by the spliced domain. These oligonucleotides therefore allow the identification of the spliced form in the RNAs of a test sample through hybridization;

(d) repeating steps (a) to (c) listed above with other proteins or splicing events characteristic of apoptotic conditions ;

(e) transferring upon a first suitable support one or a plurality of oligonucleotides specific to apoptotic forms of messengers identified hereinabove and, upon another suitable support, one or a plurality of oligonucleotides specific to non-apoptotic forms."

"Other similar libraries can be generated using oligonucleotides specific to different pathophysiological states (neurodegeneration, toxicity, proliferation, etc.), thus broadening the range of applications.

Alternative intron or exon libraries can also be in the form of computerized data base systems compiled by systematically analyzing databases in which information about genomes of individual organisms, tissues or cell cultures is recorded. In such a case, the data obtained by elaboration of such virtual databases may be used to generate oligonucleotide primers that will serve in testing two pathophysiological conditions in parallel.

The computerized databases may further be used to derive versatile nucleotide probes, representative of a given class of proteins, or specific of a particular sequence."

It is thus submitted respectfully that the specification provides numerous species of the claimed genus as well as detailed methods allowing the obtaining of further species in a very reproducible manner.

c) The specification not only teaches methods of obtaining nucleic acids that correspond to spliced regions, as correctly pointed out by the Examiner, but also clearly teaches products comprising such nucleic acids as presently claimed.

For instance, in **Example 3**, libraries of spliced nucleic acids are produced and deposited on supports, to generate products as claimed. In particular, page 54, lines 4-6, disclose that "*the resulting cloned cDNAs were amplified by PCR, electrophoresed on agarose gels and then transferred to a nylon filter*" (emphasis added). As recited in claim 65, nylon filters represent an example of supports within the scope of the present invention. Figure 12 shows the results of hybridisation experiments using such products and further illustrates the claimed invention.

Example 4 also clearly illustrates the deposit of the cloned nucleic acids on solid supports. As stated, for instance, page 54 lines 33-34 : "*the library pairs are advantageously deposited on a support.*" The term "*support*" is expressly quoted in Figures 13-15. In Example 4.5, spliced clones are deposited on a membrane and used in hybridization experiments to identify novel genes involved in apoptosis. The results are depicted in Figure 16 and clearly illustrate how to perform the claimed invention.

As indicated page 58, lines 2-5, the invention also encompasses "*an array of alternative exons or introns*" and allow "*the design of nucleic acid probes or oligonucleotide primers in order to characterize alternative splicing forms which distinguish two different pathophysiological conditions.*"

Accordingly, the teaching in the specification is clearly not limited to methods and approaches for obtaining nucleic acids, but also clearly encompasses and discloses products comprising such nucleic acids attached to a support material.

Based on the description contained in the patent would clearly convey to the skilled artisan that the inventors were in possession of the claim invention at the time of filing and would place the skilled artisan in a position to carry out the invention the whole breadth of the claims, i.e., to identify splicing events, produce polynucleotides specific for such splicing events and arrange such polynucleotides on a support, as illustrated in the working examples. It is therefore submitted that the specification complies with the requirements of 35 U.S.C. § 112, first paragraph, and withdrawal of the corresponding rejection is respectfully requested.

Claim rejection under 35 U.S.C. § 112, second paragraph

Claims 60-63 and 72-90 have been rejected under 35 U.S.C. § 112, second paragraph, for lack of clarity. In rendering the rejection, the Examiner notes that the claims contain process steps to define products. It is believed that the claims as filed also contain features defining the products by their nature and properties. Furthermore, in order to promote the progress of the prosecution of this application, claims 60-62, 72-73, 75-76, 80-81, 83-84 and 88-89 have been amended to further provide that the nucleic acid molecules comprise either cDNAs or single-stranded oligonucleotides. It is thus believed that the rejection has been overcome and withdrawal thereof is respectfully requested.

Claim rejection under 35 U.S.C. § 102

Claim 58 has been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Chee et al. Applicants respectfully traverse the rejection.

Chee et al. relates to oligonucleotide probes for detecting single nucleotide variations in a reference sequence. As pointed out by the Examiner, Chee more particularly discloses probes to CFTR 10 exon.

However, this reference does not anticipate the claimed invention. Indeed, Chee does not disclose a product comprising at least two nucleic acid molecules specific for a distinct exon or intron of a gene. Chee discloses probes specific for mutations at a particular position in exon 10 of the CFTR gene (the ΔF508 mutation). These probes would allow the identification of molecules comprising or lacking said mutation at said specific position. However, these probes do not allow the determination of the presence and absence of an exon or intron in a gene, and

Chee et al does not relate to nor suggests, in any way, a method based on the monitoring of differential alternative exons and introns splicings. Withdrawal of the rejection is thus respectfully requested.

Claim rejections under 35 U.S.C. § 103

- *Rejection over Siddique in view of Chee et al.*

Claim 59 has been rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Siddique et al. in view of Chee et al. Applicants respectfully traverse the rejection.

Siddique relates to the identification of a specific protein, termed α-tocopherol transport protein ("αTTP"). The reference analyses the structure of the corresponding gene and, for this purpose, discloses particular primers to amplify specific portions of the gene. However, the primers used are not "complementary to" an exon-exon or to an exon-intron junction region, as required by claim 59. Rather, the Siddique primers match flanking sequences of such potential junction regions and can only be used in amplification reactions to generate amplification products comprising a junction region. Accordingly, such primers are not complementary to an exon-exon or to an exon-intron junction region and, upon immobilization on a support, cannot serve to determine the presence of a junction. Furthermore, as correctly pointed out by the Examiner, Siddique does not teach a solid support.

The deficiencies in Siddique are not cured by Chee et al. As indicated above, Chee et al. relates to oligonucleotide probes for detecting single nucleotide variations in a reference sequence. For the reasons explained above, using the specific primers as disclosed in Siddique on a support would not allow the detection of splicing junctions, because said primers are not complementary to splice junctions. Furthermore, Siddique et al relates to a particular gene, does not indicate whether this gene is subject to any alternative splicing, and does not suggest any product as presently claimed comprising a plurality of oligonucleotides specific for distinct junction regions.

The instant invention relates to a novel concept of genetic analysis and functional genomics, and provides novel products for performing such analyses. None of the prior art of record relates to or suggests, in any way, a method based on the monitoring of differential alternative exons and introns splicings. No prior art of record discloses or suggests products, as

presently claimed, comprising a plurality of nucleic acid sequences specific for splicings events, allowing the monitoring of differential alternative exons and introns splicings in a sample.

Applicants submit that the instant invention provides for the first time methods for the systemic extraction and analysis of qualitative genomic alterations that represent a signature of a particular physiological status and/or cell based on nucleic acid splicings.

It is believed that none of the prior art references, either alone or in combination, suggested the instantly claimed invention, which therefore meets the requirements of 35 U.S.C. § 103.

- *Rejection over Huo et al. in view of Chee et al.*

Claims 61-63, 65-70, 90-92 have been rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Huo et al. in view of Chee et al. Applicants respectfully traverse the rejection.

Huo relates to a method of identifying sequence differences in a cell. Hybrids are formed between two samples from the same cell and mismatch-containing hybrids are cleaved to identify genetic differences. This reference, however, fails to disclose the production and use of any nucleic acid molecule specific for splicing events. This reference fails to disclose or suggest any splice junction oligonucleotides or their uses to monitor alternative exon splicings, as recited in claim 61. This reference does not disclose any product comprising a plurality of nucleic acids attached to a support as recited in the claims, and does not teach how to make such products.

The deficiencies in Huo cannot be cured by Chee et al. Indeed, as indicated above, Chee et al. relates to oligonucleotide probes for detecting single nucleotide variations in a reference sequence. There is no suggestion in Chee to monitor alternative exons and there is no teaching or description in Huo of any splice oligonucleotides.

No prior art of record discloses or suggests products, as presently claimed, comprising a plurality of nucleic acid sequences specific for splicings events, allowing the monitoring of differential alternative exons and introns splicings in a sample. The instant invention provides for the first time methods for the systemic extraction and analysis of qualitative genomic alterations that represent a signature of a particular physiological status and/or cell based on nucleic acid splicings. None of the prior art references, either alone or in combination, suggest the instantly claimed invention, which therefore meets the requirements of 35 U.S.C. § 103.

- *Rejection over Huo et al. in view of Chee et al. and further in view of Sidransky*

Claim 64 has been rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Huo et al in view of Chee et al. and in further view of Sidransky et al. Applicants respectfully traverse the rejection.

Claim 64 relates to products wherein the nucleic acid molecules on the support comprise an autologous library characteristic of alternative forms of splicings occurring between messenger and pre-messenger RNAs.

The content of Huo et al. and Chee et al. has been discussed extensively above. As indicated, none of these documents discloses or suggests products, as presently claimed, comprising a plurality of nucleic acid sequences specific for splicing events, allowing the monitoring of differential alternative exons and introns splicings in a sample.

Sidransky et al. relates to a particular gene transcript. While it is stated that pre-mRNAs contain multiple introns which are excised by RNA splicing, this certainly does not render the invention obvious. First of all, there would be no motivation for a skilled artisan to combine the teaching of Sidransky with the other quoted references. Sidransky relates to a particular gene transcript and certainly not to a general method or composition for monitoring exons. Second, while the reference very briefly states that that pre-mRNAs contain multiple introns which are excised by RNA splicing, this does not teach or suggest how to monitor exons/introns.

The instant invention provides for the first time methods for the systemic extraction and analysis of qualitative genomic alterations that represent a signature of a particular physiological status and/or cell based on nucleic acid splicings. None of the prior art references, either alone or in combination, suggest the instantly claimed invention, which therefore meets the requirements of 35 U.S.C. § 103.

- *Rejection over Huo et al. in view of Chee et al. and in further view of Korneluk*

Claim 71 has been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Huo et al. in view of Chee et al. and in further view of Korneluk et al. Applicants respectfully traverse the rejection.

Claim 71 relates to products comprising nucleic acid molecules specific form alternative forms of splicings characteristic of a toxicity status.

The content of Huo et al. and Chee et al. has been discussed extensively above. As indicated, none of these documents discloses or suggests products, as presently claimed, comprising a plurality of nucleic acid sequences specific for splicing events, allowing the monitoring of differential alternative exons and introns splicings in a sample.

Korneluk et al relates to XAF genes and corresponding proteins. This reference, however, does not cure the deficiencies in Huo and Chee, which also do not teach a product comprising a plurality of nucleic acids, as presently claimed. There would be no motivation for a skilled artisan to combine the teaching of Korneluk with the other quoted references since Korneluk relates to XAF nucleic acids and not to a general method or composition for monitoring exons.

The instant invention provides for the first time methods for the systemic extraction and analysis of qualitative genomic alterations that represent a signature of a particular physiological status and/or cell based on nucleic acid splicings. None of the prior art references, either alone or in combination, suggest the instantly claimed invention, which therefore meets the requirements of 35 U.S.C. § 103.

- *Rejection over Huo et al. in view of Chee et al. and in further view of Ludwig et al.*

Claim 93 has been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Huo et al. in view of Chee et al. and in further view of Ludwig et al. Applicants respectfully traverse the rejection.

Claim 93 relates to products comprising, immobilized on a support, a library of microorganisms transformed by a particular nucleic acid library.

The content of Huo et al. and Chee et al. has been discussed extensively above. As indicated, none of these documents discloses or suggests products, as presently claimed, comprising a plurality of nucleic acid sequences specific for splicing events, allowing the monitoring of differential alternative exons and introns splicings in a sample.

Ludwig relates to methods for pre-selecting recombinant clones. This reference, however, cannot cure the deficiencies in Huo and Chee. Indeed, this reference fails to teach or disclose any library of splicings and is totally silent about monitoring exons or introns. The mere description of a generic technique for selecting recombinant cellular clones cannot render obvious the present invention which stems from the design of specific nucleic acid molecules. Also, there would be no motivation for a skilled artisan to combine the teaching of Ludwig with the other quoted references since they relate to remote techniques.

No prior art based objection has been raised against claims 60 and 72-89.

As indicated above, the present invention provides for the first time products and methods for the systemic extraction and analysis of qualitative genomic alterations that represent a signature of a particular physiological status and/or cell based on nucleic acid splicings. None of the prior art references, either alone or in combination, suggest the instantly claimed invention, which therefore meets the requirements of 35 U.S.C. § 103.

CONCLUSION

In light of the foregoing amendments and remarks, Applicants submit that the claims are novel and inventive over the prior art and respectfully request favourable reconsideration of the present application. In particular, it is believed that the claims are now in condition for allowance and a notification to that effect is earnestly solicited.

Applicant notes that the Office action was mailed to the incorrect address. Effective immediately, please address all communication in this application to:

Kristina Bieker-Brady, Ph.D.
Clark & Elbing LLP
101 Federal Street
Boston, MA 02110

Enclosed is a Petition to extend the period for replying to the Office Action for one month, to and including December 30, 2002, since December 28th falls on a Saturday. Also

enclosed is a check in the amount of $55.00 for the payment of the petition fee as required by 37 C.F.R. 1.17(a)(1). If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: December 30, 2002

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"VERSION WITH MARKINGS TO SHOW CHANGES MADE"

In the specification:

Paragraph beginning on page 16, line 17 has been amended as follows:

In this respect, so as to increase the priming events on the RNAs to be cloned, reactions may be carried out in parallel with oligonucleotides such as:

GAGAAGCGTTATNNNNNNNAGGT (oligonucleotides A) (SEQ ID NO: 1; X = T)

GAGAAGCGTTATNNNNNNNAGGA (oligonucleotides B) (SEQ ID NO: 1; X = A)

GAGAAGCGTTATNNNNNNNAGGC (oligonucleotides C), (SEQ ID NO: 1; X = C),

GAGAAGCGTTATNNNNNNNAGGG (oligonucleotides D) (SEQ ID NO: 1; X = G)

each oligonucleotide population (A, B, C, D) being able to be used alone or in combination with another.

Paragraph beginning on page 48, line 34 has been amended as follows:

The PCR products are cloned into the pGEM-T vector (Promega) with a floating T at the 3' ends so as to simplify cloning of the fragments derived from the activity of Taq polymerase. After transformation in competent JM109 bacterial (Promega), the resulting colonies are transferred to nitrocellulose filters, and hybridized with probes derived from the products of PCR carried out on total cDNA from growing cells on the one hand and in anoikis on the other hand. The same oligonucleotides GAGAAGCGTTATNNNNNCCA (SEQ ID NO: 4) are used for these PCR reactions. In a first experimental embodiment, 34 clones preferentially hybridizing with the probe from cells in apoptosis and 13 clones preferentially hybridizing with the probe from growing cells were located.

In the claims:

Claims 60-62, 75, 76, 83 and 84 have been amended as follows:

60. (Amended) The product of claim 58 or 59, wherein said plurality of different nucleic acid molecules comprises cDNA molecules and is obtained by a method of identifying or cloning differentially spliced nucleic acids, said method comprising:

a) hybridizing a plurality of different RNAs derived from a first sample, wherein the composition or sequence of the RNAs is at least partially unknown, with a plurality of different cDNAs derived from a second sample, wherein the composition or sequence of the cDNAs is at least partially unknown; and

b) identifying or cloning, from the hybrids formed in a), a population of nucleic acids comprising an unpaired region, said cloned or identified nucleic acids comprising an unpaired region corresponding to portions of genes that are differentially spliced between said samples.

61. (Amended) The product of claim 58, wherein said plurality of different nucleic acid molecules comprises single-stranded oligonucleotides comprising a sequence complementary to and specific for an exon or an intron of a gene, and wherein said oligonucleotides are [is] obtained by a method comprising:

(a) identifying a splicing event characteristic of a physiopathological condition and determining the sequence of the spliced domain,

(b) synthesizing one or several single-stranded oligonucleotides complementary to and specific for said domain, and

(c) repeating steps (a) and (b) above with at least a second splicing event characteristic of said physiopathological condition.

62. (Amended) The product of claim 59, wherein said plurality of different nucleic acid molecules comprises single-stranded oligonucleotides comprising a sequence complementary to and specific for junction region of a gene or RNA, and wherein said oligonucleotides are [is] obtained by a method comprising:

(a) identifying a splicing event characteristic of a physiopathological condition and determining the sequence of the spliced domain,

(b) synthesizing one or several single-stranded oligonucleotides complementary to and specific for a junction region formed by the splicing or absence of splicing of said domain and

(c) repeating steps (a) and (b) above with at least a second splicing event characteristic of said physiopathological condition.

72. (Amended) A product for evaluating the toxicity of a compound or treatment to a cell, tissue or organism, the product comprising a support material and a plurality of different nucleic acid molecules selected from cDNA molecules and single-stranded oligonucleotides, said nucleic acid molecules being attached to said support material, the nucleic acid molecules comprising nucleic acid molecules containing a sequence that is complementary to and specific for introns or exons that are retained or spliced in a cell treated by a reference toxic compound or treatment, said product comprising at least two nucleic acid molecules complementary to and specific for a distinct exon or intron of the same gene and said product allowing, when contacted with a sample containing nucleic acids under condition allowing hybridisation to occur, the determination of the presence or absence of said exon or intron of said gene in said sample.

73. (Amended) A product for evaluating the toxicity of a compound or treatment to a cell, tissue or organism, the product comprising a support material and a plurality of different nucleic acid molecules selected from cDNA molecules and single-stranded oligonucleotides, said nucleic acid molecules being attached to said support material, the nucleic acid molecules comprising nucleic acid molecules containing a sequence that is complementary to and specific for exon-exon or exon-intron junction regions of genes or RNAs that are spliced in a cell treated by a reference toxic compound or treatment, said product comprising at least two nucleic acid molecules complementary to and specific for a distinct junction region of the same or a different gene or RNA, and said product allowing, when contacted with a sample containing nucleic acids under conditions allowing hybridisation to occur, the determination of the presence or absence of said junction regions in said sample.

75. (Amended) The product of claim 72, wherein said plurality of different nucleic acid molecules comprises single-stranded oligonucleotides comprising a sequence complementary to and specific for an exon or an intron retained or spliced in a cell treated by a reference toxic compound or treatment, and wherein said oligonucleotides are [is] obtained by a method comprising:

(a) identifying a splicing event characteristic of a cell treated by a reference toxic compound or treatment and determining the sequence of the spliced domain,

(b) synthesizing one or several single-stranded oligonucleotides complementary to and specific for said domain, and

(c) repeating steps (a) and (b) above with at least a second splicing event characteristic of said toxic condition.

76. (Amended) The product of claim 73, wherein said plurality of different nucleic acid molecules comprises single-stranded oligonucleotides comprising a sequence complementary to and specific for a junction region of a gene or RNA spliced in a cell treated by a reference toxic compound or treatment, and wherein said oligonucleotides are [is] obtained by a method comprising:

(a) identifying a splicing event characteristic of a cell treated by a reference toxic compound or treatment and determining the sequence of the spliced domain,

(b) synthesizing one or several single-stranded oligonucleotides complementary to and specific for a junction region formed by the splicing or absence of splicing of said domain and

(c) repeating steps (a) and (b) above with at least a second splicing event characteristic of said toxic condition.

80. (Amended) A product for evaluating the therapeutic efficacy of a compound to a cell, tissue or organism, the product comprising a support material and a plurality of different nucleic acid molecules selected from cDNA molecules and single-stranded oligonucleotides, said nucleic acid molecules being attached to said support material, the nucleic acid molecules comprising nucleic acid molecules containing a sequence that is complementary to and specific for introns or exons that are retained or spliced in a cell treated by a reference therapeutic compound, said product comprising at least two nucleic acid molecules complementary to and specific for a distinct exon or intron of the same gene and said product allowing, when contacted with a sample

containing nucleic acids under conditions allowing hybridisation to occur, the determination of the presence or absence of said exon or intron of said gene in said sample.

81. (Amended) A product for evaluating the therapeutic efficacy of a compound to a cell, tissue or organism, the product comprising a support material and a plurality of different nucleic acid molecules selected from cDNA molecules and single-stranded oligonucleotides, said nucleic acid molecules being attached to said support material, the nucleic acid molecules comprising nucleic acid molecules containing a sequence that is complementary to and specific for exon-exon or exon-intron junction regions of genes or RNAs that are spliced in a cell treated by a reference therapeutic compound, said product comprising at least two nucleic acid molecules complementary to and specific for a distinct junction region of the same or a different gene or RNA, and said product allowing, when contacted with a sample containing nucleic acids under condition allowing hybridisation to occur, the determination of the presence or absence of said junction regions in said sample.

83. (Amended) The product of claim 80, wherein said plurality of different nucleic acid molecules comprises single-stranded oligonucleotides comprising a sequence complementary to and specific for an exon or an intron retained or spliced in a cell treated by a reference therapeutic compound, and wherein said oligonucleotides are [is] obtained by a method comprising:

(a) identifying a splicing event characteristic of a cell treated by a reference therapeutic compound and determining the sequence of the spliced domain,

(b) synthesizing one or several single-stranded oligonucleotides complementary to and specific for said domain, and

(c) repeating steps (a) and (b) above with at least a second splicing event characteristic of said therapeutic condition.

84. (Amended) The product of claim 81, wherein said plurality of different nucleic acid molecules comprises single-stranded oligonucleotides comprising a sequence complementary to and specific for a junction region of a gene or RNA spliced in a cell treated by a reference therapeutic compound, and wherein said oligonucleotides are [is] obtained by a method comprising:

(a) identifying a splicing event characteristic of a cell treated by a reference therapeutic compound and determining the sequence of the spliced domain,

(b) synthesizing one or several single-stranded oligonucleotides complementary to and specific for a junction region formed by the splicing or absence of splicing of said domain and

(c) repeating steps (a) and (b) above with at least a second splicing event characteristic of said therapeutic condition.

88. (Amended) A product for evaluating the responsiveness of a subject to a compound or treatment, the product comprising a support material and a plurality of different nucleic acid molecules selected from cDNA molecules and single-stranded oligonucleotides, said nucleic acid molecules being attached to said support material, the nucleic acid molecules comprising nucleic acid molecules containing a sequence that is complementary to and specific for introns or exons that are retained or spliced in a cell from a responsive subject treated by a reference therapeutic compound or treatment, said product comprising at least two nucleic acid molecules complementary to and specific for a distinct exon or intron of the same gene and said product allowing, when contacted with a sample containing nucleic acids under condition allowing hybridisation to occur, the determination of the presence or absence of said exon or intron of said gene in said sample.

89. (Amended) A product for evaluating the responsiveness of a subject to a compound or treatment, the product comprising a support material and a plurality of different nucleic acid molecules selected from cDNA molecules and single-stranded oligonucleotides, said nucleic acid molecules being attached to said support material, the nucleic acid molecules comprising nucleic acid molecules containing a sequence that is complementary to and specific for exon-exon or exon-intron junction regions of genes or RNAs that are spliced in a cell from a responsive subject treated by a reference therapeutic compound or treatment, said product comprising at least two nucleic acid molecules complementary to and specific for a distinct junction region of the same or a different gene or RNA, and said product allowing, when contacted with a sample containing nucleic acids under conditions allowing hybridisation to occur, the determination of the presence or absence of said junction regions in said sample.